Abstract
Caffeine can improve exercise performance when it is ingested at moderate doses (3–6 mg/kg body mass). Caffeine also has an effect on the central nervous system (CNS), and it is now recognized that most of the performance-enhancing effect of caffeine is accomplished through the antagonism of the adenosine receptors, influencing the dopaminergic and other neurotransmitter systems. Adenosine and dopamine interact in the brain, and this might be one mechanism to explain how the important components of motivation (i.e. vigor, persistence and work output) and higher-order brain processes are involved in motor control. Caffeine maintains a higher dopamine concentration especially in those brain areas linked with ‘attention’. Through this neurochemical interaction, caffeine improves sustained attention, vigilance, and reduces symptoms of fatigue. Other aspects that are localized in the CNS are a reduction in skeletal muscle pain and force sensation, leading to a reduction in perception of effort during exercise and therefore influencing the motivational factors to sustain effort during exercise. Because not all CNS aspects have been examined in detail, one should consider that a placebo effect may also be present. Overall, it appears that the performance-enhancing effects of caffeine reside in the brain, although more research is necessary to reveal the exact mechanisms through which the CNS effect is established.

Introduction
Caffeine can improve endurance performance when it is ingested at low–moderate dosages (3–6 mg/kg body mass); no further enhancement in performance is found when it is consumed at higher dosages (≥9 mg/kg) [1]. Caffeine supplementation is beneficial for sustained maximal endurance exercise, especially for time trial performance [1, 2]. Caffeine is also beneficial for high-intensity
exercise, including team sports such as soccer and rugby, both of which are categorized by intermittent activity within a period of prolonged duration [3, 4]. The literature is equivocal when considering the effects of caffeine supplementation on strength-power performance, and additional research in this area is warranted [1, 5].

The effects of caffeine in reducing fatigue and increasing wakefulness and alertness have been recognized for a very long time. These properties have been targeted by shift workers, long-haul truck drivers, members of the military forces, athletes, and other populations who need to fight fatigue or prolong the capacity to undertake their occupational activities [2, 6, 7]. It has been shown that caffeine can enhance vigilance during bouts of extended exhaustive exercise, as well as periods of sustained sleep deprivation. The effects on attention, vigilance and alertness are established through the central nervous system (CNS), and several possible pathways and neurotransmitter systems are probable candidates for its action in the brain.

In this paper, we will discuss the possible mechanisms of how caffeine can influence performance through actions on the CNS.

**How Does Caffeine Influence the Brain?**

We are all aware of the fact that we need that morning cup of coffee, our daily dose of caffeine, to get started. We are more alert, more awake and feel better. Is this action really happening in the brain, or do we think caffeine works to keep us awake?

Caffeine is known to be a CNS stimulant, causing increased wakefulness, alertness, arousal, and vigilance as well as elevations of mood. Caffeine is quickly absorbed through the gastrointestinal tract. It is also lipid soluble and crosses the blood-brain barrier without difficulty.

Caffeine is an adenosine receptor antagonist, which means that it will influence the action of adenosine in a negative way [8]. The brain has a large number of adenosine receptors. The major known effect of adenosine is to decrease the concentration of many neurotransmitters, including serotonin, dopamine (DA), acetylcholine, norepinephrine, and glutamate. Caffeine blocks the adenosine receptors and opposes the effects of adenosine and therefore increases the concentration of these neurotransmitters in the CNS [8]. Increased actions of these neurotransmitters result in positive effects on vigilance, wakefulness, alertness, etc. [9].

Depending on the neurotransmitter system, caffeine can affect different brain areas with different functions. The most direct ways for caffeine to influ-
ence muscular performance is through its influence on the motor pathways (fig. 1). The CNS motor output originates from the pre-motor, supplementary motor and primary motor cortex neurons. The motor signal will travel through the corticospinal tract and the spinal cord to the muscle where contraction (exercise) takes place. A closed loop feedback system will create ascending signals through several possible pathways, influencing motor and other brain areas (fig. 1). Sensory afferents travel back via the spinal cord to the brain stem and the thalamus, which can be considered as the switch board for the afferent signals, and the cerebellum, which is important for motor function. From here, the signal travels to several key nuclei important in motor control such as the basal ganglia which are very rich in DA, the nucleus accumbens and the somatosensory cortices finally closing the feedback loop (fig. 1). All these brain areas can indirectly affect performance via projections to the motor cortex.

Several lines of evidence indicate that DA and adenosine systems interact in the brain. Both DA and adenosine have several receptor types; for DA the D2 receptors and for adenosine the A2A receptors play an important role in the stimulatory effect of caffeine. Striatal areas such as the neostriatum and nucleus

Fig. 1. Most direct ways for caffeine to effect muscular performance.
accumbens are very rich in adenosine A<sub>2A</sub> receptors, and there is a functional interface between striatal DA D<sub>2</sub> and adenosine A<sub>2A</sub> receptors. This interaction has frequently been studied with regard to neostriatal motor functions. Nucleus accumbens DA is a critical component of the brain circuitry involved in behavioral activation and effort-related behavioral processes [10]. This means that both motor effects and motivational aspects will be influenced when adenosine receptors are blocked through caffeine, creating a greater dopaminergic drive.

This ‘motor drive’ effect was nicely shown by Davis et al. [11] who examined the effects of direct injections of caffeine into the brains of rats on their ability to run to exhaustion on a treadmill. In this controlled study, rats were injected with either vehicle (placebo), caffeine, an adenosine receptor agonist, or caffeine and the adenosine receptor agonist together. Rats ran 80 min in the placebo trial, 120 min after caffeine injection and only 25 min with adenosine receptor agonist. When caffeine and adenosine receptor agonist were given together, run time was not different from placebo. When the study was repeated with peripheral intraperitoneal injections instead of brain injections, there was no effect on run performance. The authors concluded that caffeine delayed fatigue through CNS effects, in part by blocking adenosine receptors [11].

But the influence of caffeine on exercise performance is not only situated in the ‘pure’ motor areas of the brain, as several other mechanisms can be responsible for the effect that caffeine may (or may not) have on exercise performance in humans.

DA and adenosine systems in the brain, possibly in nucleus accumbens, interact in the regulation of instrumental response output and effort-related choice behavior, probably because of the interaction between adenosine A<sub>2A</sub> and DA D<sub>2</sub> receptors. This is likely related to the co-localization of these receptors on the same population of striatal and accumbens neurons. Characterization of the neurochemical mechanisms involved in regulating behavioral activation and effort-based choice behavior can shed light on these important facets of motivation, and also may serve to illustrate the relation between activational aspects of motivation (i.e. vigor, persistence and work output) and higher-order processes involved in motor control. Activational aspects of motivated behavior are highly adaptive because they enable organisms to surmount work-related response costs or obstacles that limit access to significant stimuli. This aspect is very important in sport performance because fatigue, effort and motivation are closely related in these specific brain areas.

The influence of caffeine on CNS functioning could be responsible for the positive effects on exercise performance. Some of these elements have been shown in experimental trials, while others still need further exploration.
Caffeine Improves Sustained Attention (Vigilance) and Reduces Symptoms of (Mental) Fatigue

Miridakis et al. [12, 13] conducted a double-blind, placebo-controlled experiment to compare the sensitivity to change of the cognitive performance and mood measures of mental energy following consumption of caffeine (100 and 200 mg). The authors defined ‘mental energy’ as the ability to perform mental tasks, the intensity of feelings of energy/fatigue, and the motivation to accomplish mental and physical tasks. Nine cognitive and five mood measures were used to quantify the effects of consuming 2 different doses of caffeine. As expected, caffeine attenuated the reduced feelings of energy and increased feelings of fatigue that occurred in the placebo condition. The sensitivity to 100 mg of caffeine was statistically different among the two energy measures, but not among the fatigue measures. The sensitivity to 200 mg of caffeine was statistically not different among the two energy or fatigue measures. Both doses of caffeine produced uniform changes among measures of cognitive performance, the Visual Analogue Scale mental energy measure and the Profile Of Mood State (POMS) vigor measure (fig. 2). It seems that a small dose (100 mg) of caffeine is enough to produce small-to-moderate size

Fig. 2. Caffeine improves mood and performance and lowers the fatigue score in a dose-dependent manner. Both doses of caffeine produced uniform changes among measures of cognitive performance, the Visual Analogue Scale (VAS) mental energy measure and the Profile Of Mood State (POMS) vigor measure. Adapted from Maridakis et al. [12, 13].

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improvements in stimulus response, improved target identification, and reductions in false alarms. Caffeine also improved mood and performance, and subjects scored better on a reaction time test and made fewer errors during the test.

The monoamines serotonin, DA and noradrenaline play a key role in signal transduction between neurons and exercise-induced changes in the concentrations of these neurotransmitters (especially serotonin and DA), and have been linked to central fatigue [9]. Although 'central fatigue' was originally linked with an increased serotonergic drive, Davis and Bailey [14] stated that not only increases in serotonin but an interaction between serotonin and DA would influence CNS fatigue, with a low ratio favoring improved performance and a high ratio decreasing motivation and augmenting lethargy and consequently decreasing performance.

**Caffeine Reduces Skeletal Muscle Pain, Force Sensation and Perception of Effort during Exercise, and Increases Motivation to Sustain Effort**

Moderate- to high-intensity exercise results in transient, naturally occurring muscle pain that is located in the activated musculature [15]. Caffeine is a non-selective adenosine antagonist with established anti-nociceptive actions. Muscle adenosine concentration is increased with muscle contractions [10], but whether adenosine plays a role in perceptions of naturally occurring skeletal muscle pain during exercise is unclear. The pain-reducing effect of blocking adenosine can be located both at the peripheral and central level, although the final perception and processing of the pain signal occurs through the CNS. Several studies have demonstrated that ingestion of caffeine significantly reduced muscle pain intensity ratings in males and females during 30 min of cycling on an ergometer at \( \sim 60\% \text{ VO}_{2\text{peak}} \) [15, 16] (fig. 3). In this study, caffeine doses of 5 and 10 mg/kg were used, and the ratings of perceived exertion (RPE) ratings were low in all trials. Several possible mechanisms exist for the caffeine-induced reduction in muscle pain during exercise. The hypoalgesia might stem from caffeine acting on peripheral or central adenosine receptors involved in the nociceptive system [17]. Alternatively, caffeine might indirectly influence the nociceptive system, for example, by altering muscle sensory processes. Separating the peripheral and central effects of caffeine in studies with humans is difficult, as caffeine has the potential to affect many tissues at once.

Also local muscle fatigue will be influenced by caffeine ingestion. Plaskett and Cafarelli [18] studied 15 subjects in a randomized, double-blind, repeated-
measures experiment to determine caffeine’s ergogenic effects on neuromuscular variables that would contribute to increased endurance capacity. Subjects performed repeated submaximal isometric contractions (50% maximal voluntary contraction) of the right quadriceps to the limit of endurance 1 h after oral caffeine administration (6 mg/kg). Time to reach the limit of endurance increased by 17% after caffeine administration compared with the placebo trial. The results of this experiment showed that caffeine reduced force sensation during the first 10–20 s of the contraction. The rapidity of this effect suggests that caffeine exerts its effects neurally. The authors concluded that the caffeine-induced increase in performance may have been caused by a willingness to maintain near-maximal activation longer because of alterations in muscle sensory processes.

A consistent outcome of caffeine ingestion during exercise testing, regardless of mode, intensity, or duration of exercise, is an alteration in participants’ perceptual response. This alteration has been manifested as either an increase in work output at a given RPE or effort sense or, more typically, a reduced RPE at a constant exercise intensity. Doherty and Smith [19] published a meta-analysis that clearly showed that the mean effect size for caffeine’s influence on RPE during whole-body exercise is significantly greater than zero. In comparison to placebo, this effect represents almost a 6% reduction in the RPE during constant rate exercise. This evidence quantifies reports in the literature that caffeine has a noticeable effect on RPE.

This ‘motivational’ aspect of caffeine is probably through its stimulating effect on the dopaminergic system. It has been demonstrated that a moderate

![Graph showing the effects of caffeine on RPE during exercise](image-url)
dose of the DA stimulant D-amphetamine increases willingness to exert effort in healthy young adults, particularly when reward probability is low. Adenosine receptors interact with DA receptors to influence both the reinforcing effects of psychostimulants and effort exerted for rewards.

Caffeine Increases Tremor

Accuracy is important in most sports, but it is known that ‘overinfluencing’ the motor areas of the brain might have negative effects. Fine motor skills are important in several sports and especially sports that combine these features with endurance exercise (e.g. biathlon and all the stop and go sports like football, ice and field hockey, basketball). Any overinfluencing side effects can negatively affect performance. Miller et al. [20] examined the effects of a single oral dose of caffeine at typical daily levels of consumption (1 and 3 mg caffeine/kg body mass). They found a significant increase in tremor compared to placebo at 3 but not 1 mg caffeine/kg. Although many studies have recently reported significant effects of caffeine on various cognitive and psychomotor tasks, fewer studies have reported the direct effects of caffeine on physiological tremor. This effect does not have a real importance in endurance sports; however, in sports where accuracy (biathlon, shooting, archery, basketball, etc.) plays a role, this CNS side effect of caffeine should be avoided.

Caffeine Can Have a Placebo Effect

It has also been suggested that beliefs about the effects of caffeine or caffeine expectancies may factor into the performance effects of caffeine. The effects of caffeine dose and/or caffeine instructions on performance (e.g. reaction time) or subjective outcomes (e.g. arousal) are more pronounced among participants who hold expectancies that caffeine produces those effects. This was nicely shown in a study from Harrel and Juliano [21]. After overnight caffeine abstinence, participants were given coffee and were told either that caffeine would enhance or impair performance. This was crossed with the consumption of a placebo drink. Relative to placebo, caffeine improved reaction time and accuracy on the rapid visual information processing task, a measure of vigilance. However, among participants given placebo coffee, the ‘impair’ instructions produced better performance than the ‘enhance’ instructions. Caffeine also improved psychomotor performance as indicated by a finger tapping task with no
main effects of expectancy or interactions. These results provide evidence that subjective and behavioral outcomes of drug use at rest are influenced by the expected effects of drug.

Beedie et al. [22] showed that the placebo effect could also play an important role in the possible performance-enhancing effects of caffeine during exercise. The placebo effect – a change attributable only to an individual’s belief in the efficacy of a treatment – might provide a worthwhile improvement in physical performance. The authors explored the placebo effect in laboratory cycling performance using quantitative and qualitative methods. Six well-trained male cyclists undertook two baseline and three experimental 10-km time trials. Subjects were informed that in the experimental trials they would each receive a placebo, 4.5 mg/kg caffeine, and 9.0 mg/kg caffeine, randomly assigned. However, placebos were administered in all experimental conditions (fig. 4).

Surprisingly, a dose-response relationship was evident in experimental trials, with subjects producing 1.4% less power than at baseline when they believed they had ingested a placebo, 1.3% more power than at baseline when they believed they had ingested 4.5 mg/kg caffeine, and 3.1% more power than at baseline when they believed they had ingested 9.0 mg/kg caffeine. This study clearly showed that placebo effects are associated with the administration of caffeine and that these effects may directly or indirectly enhance performance in well-trained cyclists. Although these results seem to be very convincing, several points need to be raised about this experiment. There were only 6 subjects, there were no actual caffeine trials to see how large any caffeine-induced performance

**Fig. 4.** Caffeine can have a placebo effect. Subjects performed a 10-km time trial and were informed to receive a placebo, 4.5 mg/kg caffeine, and 9.0 mg/kg caffeine, randomly assigned. However, placebos were administered in all experimental conditions. Adapted from Harrell and Juliano [21].
increases would have been, and the exercise task – a 10 km time trial – would have lasted well under 20 min for well-trained cyclists – so quite short for caffeine-induced effects.

**Caffeine and Exercise Performance in Different Ambient Conditions**

Exercise capacity is enhanced after caffeine ingestion. It was originally proposed that caffeine mobilized free fatty acids from adipose tissue, resulting in higher rates of fat oxidation and sparing of muscle glycogen. More recently, this so-called ‘metabolic’ theory has been dismissed as a universal explanation for the ergogenic effect of caffeine on endurance exercise performance, and it seems that caffeine exerts its effect via central fatigue mechanisms or by facilitating muscle function. Caffeine has been shown to exert its ergogenic effects in normal ambient temperature. However, only a few studies examined the effects of adenosine receptor antagonism at high environmental temperatures. Most studies found increased core temperatures during exercise, non-attributable to metabolic heat production, as subjects did not push higher power outputs, but probably related to the influence of caffeine on the adenosine receptors and consequently DA concentration. The results on performance were divergent, with some studies showing improvements in time trial performance with caffeine ingestion [23, 24], while other studies showed that caffeine did not alter exercise performance on a preloaded time trial [25, 26]. Ganio et al. [23] showed that caffeine attenuated the perception of effort while exercising at 33°C, as was already reported at normal ambient temperature. They also found that, although caffeine improved exercise capacity, its effect on leg muscle pain was dependent on ambient temperature. Although exercise in the heat increases muscle pain compared to a cooler environment, caffeine reduced this pain [24]. Although more research is necessary to confirm these studies, it is clear that environmental conditions play an important role in the exertion of effects mediated by caffeine.

**Conclusion**

There is an extensive amount of scientific literature associated with caffeine supplementation. It is evident that caffeine is ergogenic for sport performance. It is now believed that most of the ergogenic effect of caffeine resides in the brain. Caffeine is an antagonist of the adenosine receptors and will therefore increase several neurotransmitter concentrations in the brain. One candidate mecha-
nism for this performance-enhancing effect is the influence on the dopaminergic system, by maintaining the dopaminergic drive, which is very important for motivation, sustained attention and motor drive.

**Disclosure Statement**

The authors of this chapter do not have any relationship to disclose.

**References**


